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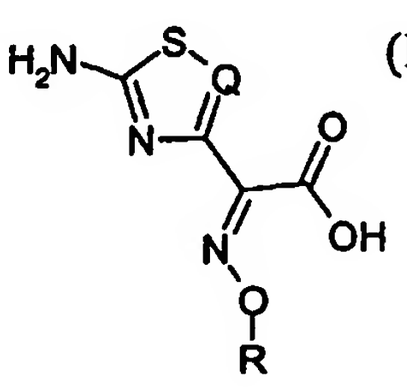
(54) Title: A PROCESS FOR THE PREPARATION OF CEPHALOSPORINS SIDE CHAINS

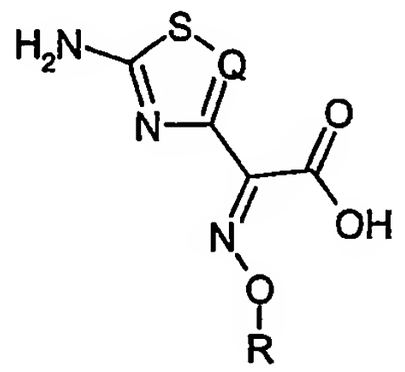


(I)

(57) Abstract: A process for the preparation of salts of organic nitrogen bases with carboxylic acids of general formula (I), wherein Q and R have the meanings defined in the disclosure, useful for the preparation of cephalosporins side chains.

A PROCESS FOR THE PREPARATION OF CEPHALOSPORINS SIDE CHAINS

The present invention relates to a process for the preparation of salts of organic nitrogen bases with carboxylic acids of formula (I)

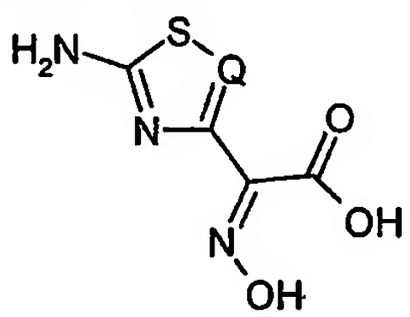


(I)

wherein:

- Q is nitrogen, a hydrocarbyl (CH) or chlorocarbyl (CCl) residue;
- R is trityl, benzhydryl or para-methoxy benzyl.

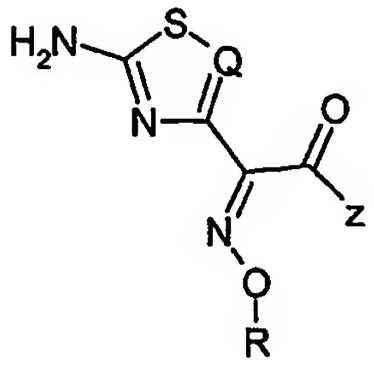
The process provides the compounds of formula (I) in high yield and purity, starting from compounds of formula (II)



(II)

wherein Q is as defined above.

The salts of acids of formula (I) with organic nitrogen bases can be easily transformed into the corresponding free acids (I) or into solvates thereof, or into compounds of general formula (III), which can either be isolated or used *in situ*, for the preparation of third and fourth generation cephalosporanic antibiotics, such as Cefdinir and Cefdaloxime



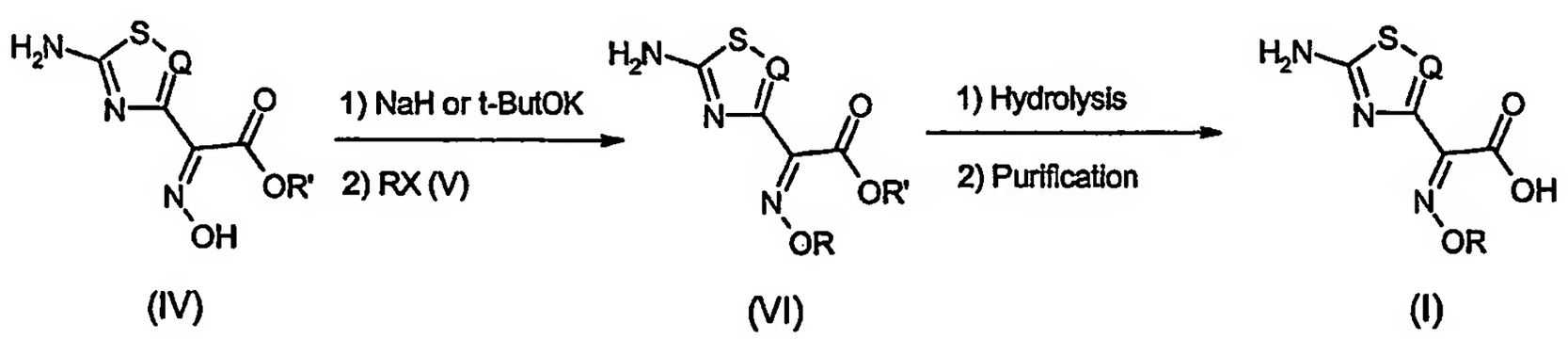
(III)

In compounds of general formula (III), Q and R are as defined above, and Z is a carboxy-activating group conventionally used in the synthesis of cephalosporanic antibiotics, such as an anhydride, an ester or an acyl halide.

TECHNICAL BACKGROUND

Carboxylic acids of formula (I) are important syntons for the preparation of third and fourth generation cephalosporins having wide spectrum activity and high potency against Gram-positive and Gram-negative microorganisms.

The more efficient methods known to date for the preparation of such compounds involve (Scheme 1) the derivatization of esters of formula (IV), by salification of the hydroxy-imino group with sodium hydride (US 4935508) or with potassium *tert*-butoxide (US 5637721) and the subsequent reaction with halides of formula (V) to obtain derivatives of formula (VI). The reaction yield usually does not exceed 80%. Compounds of formula (VI) have to undergo a hydrolysis reaction for the conversion into acids of formula (I), which have to be subsequently purified as solvates with organic amides. The overall yield usually does not exceed 60% and the process is unsuitable in terms of productivity, since it requires numerous steps to obtain suitably pure acids of formula (I) for the subsequent use.

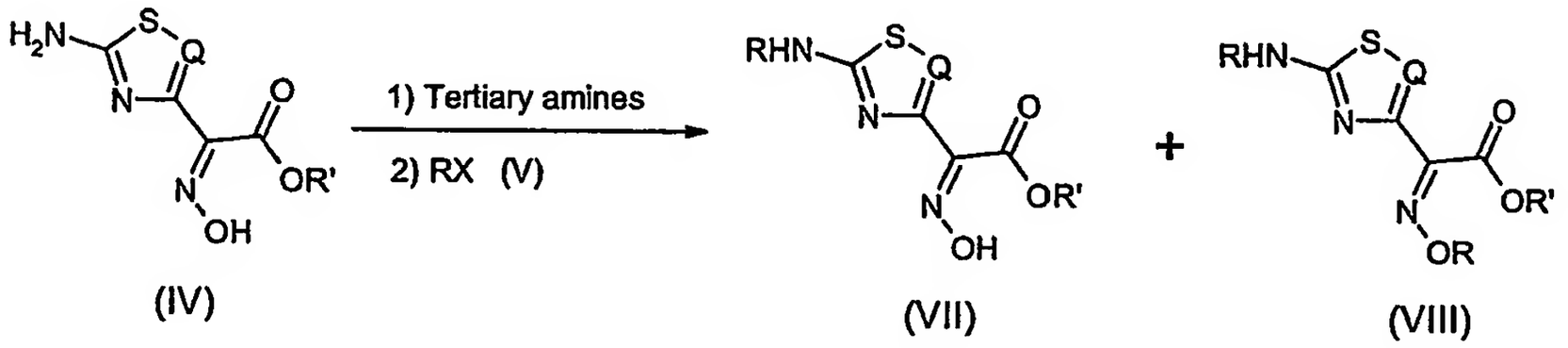


(Scheme 1)

In compounds of Scheme 1, Q and R are as defined above and R' is an alkyl residue.

As reported by Bucourt et al. in *Tetrahedron* 34, 2233 (1978), the

reaction of esters of formula (IV) with halides of formula (V) in the presence of tertiary amines (Scheme 2) yields, on the other hand, N-functionalized compounds of formula (VII) or N,O-bis-functionalized compounds of formula (VIII), in which Q, R and R' are as defined above.



(IV) (VII) (VIII)

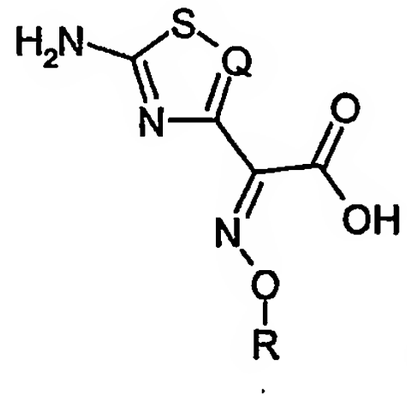
(Scheme 2)

It now has been found that the salts of the compounds of formula (I) with organic nitrogen bases can be obtained in a single step, with high yields and purity, by reacting carboxylic acids of formula (II) with halides of formula (V) in the presence of organic nitrogen bases and in industrial inert organic solvents.

Said salts can be advantageously used for the preparation of intermediates, which can be isolated or used *in situ*, for the preparation of third and fourth generation cephalosporins. In fact, thanks to their good solubility in the organic solvents traditionally used for these preparations, such as methylene chloride, ethyl acetate and tetrahydrofuran, these salts allow faster reaction rates with advantages in terms of both yield and purity of the obtained products.

DETAILED DISCLOSURE OF THE INVENTION

The present invention relates to a process for the preparation of salts of organic nitrogen bases with carboxylic acids of general formula (I)



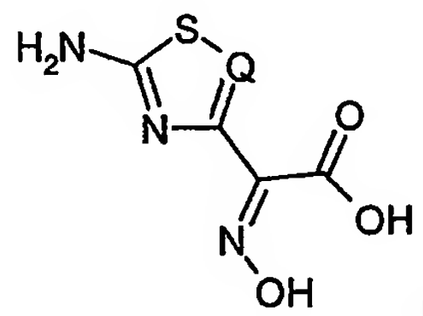
(I)

wherein

- Q is nitrogen, a hydrocarbyl (CH) or chlorocarbyl (CCl) residue, preferably nitrogen;

- R is trityl, benzhydryl or para-methoxy benzyl, preferably trityl;

which process comprises reacting a carboxylic acid of general formula (II)



(II)

wherein Q has the meaning defined above,

with a halide of formula (V)

(V) RX

wherein R has the meaning defined above and X is a halogen selected from chlorine, bromine and iodine,

in the presence of a nitrogen organic base and of an organic inert solvent.

The nitrogen organic base can be selected from tertiary amines, preferably triethylamine, tributylamine, N-ethyl diisopropylamine, N-methyl morpholine, N-methyl pyrrolidine, N-methyl piperidine, trioctylamine; amidines, preferably diazabicyclononene (DBN) and diazabicycloundecene (DBU); guanidines, preferably tetramethyl guanidine. The organic inert solvent can be selected from: halogenated hydrocarbons, preferably methylene chloride and dichloroethane; carboxylic acid esters, preferably ethyl acetate and butyl acetate; ketones, preferably acetone, diethyl ketone and methyl ethyl ketone; amides, for example N,N-dimethylformamide, N,N-dimethylacetamide, N-methylpyrrolidone; aromatic hydrocarbons, preferably benzene, toluene and xylene; ethers, preferably tetrahydrofuran, dioxane or

ethylene glycol dimethyl ether; sulfoxides or sulfones, preferably dimethylsulfoxide, dimethyl sulfone and sulfolane; or mixtures thereof.

The reaction can be carried out at temperatures ranging from -50° to 200°C, preferably from 0° to 100°C.

The halide (V) is used typically in stoichiometric amounts to compound of formula (II) or in a slight molar excess, whereas the organic base can be present in a ratio ranging from 1:1 to 1:10, preferably from 1:2 to 1:5.

The halide, which is usually added to a mixture consisting of compound of formula (II), base and organic inert solvent, can be added directly in a single or more portions, or it can be dissolved in a suitable organic solvent, for example methylene chloride, dichloroethane, toluene or xylene, and then added to the reaction mixture in a time ranging from a few minutes to some hours. The reaction is usually considered complete when the residual compound (II) is lower than 3% (HPLC analysis).

The salts, which will hereinafter be referred to as compounds (IA), usually crystallize during the reaction or upon cooling the mixture and can therefore be filtered off easily. They are usually obtained in highly pure form; if necessary, they can be further purified from any by-products (such as bis- or tris-functionalized products), by treatment with inert organic solvents selected from halogenated hydrocarbons, preferably methylene chloride or dichloroethane; aromatic hydrocarbons, preferably toluene or xylene; or mixtures thereof, optionally in the presence of cosolvents such as amides, preferably N,N-dimethylformamide, N,N-dimethylacetamide and N-methyl pyrrolidinone, at temperatures ranging from 10° to 100°C, preferably from 25° to 70°C. Salts (IA) can be further purified from traces of the starting compound (II) and any water-soluble amines hydrochlorides present by treatment with water or an aqueous solvent.

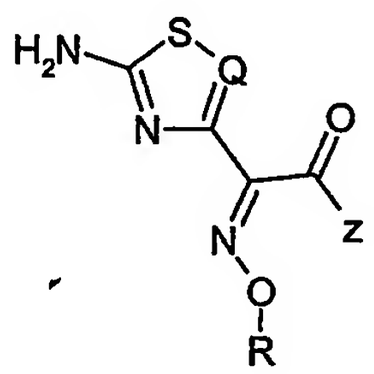
Drying of salts (IA) does not require particular procedures and can be

carried out, for example, under vacuum or by ventilation at temperatures from 30° to 100°C.

Salts (IA) can be used for the preparation of the corresponding free acids of formula (I) and the solvates thereof, for example with formamide, dimethylformamide, dimethylacetamide or N-methylpyrrolidone, according to conventional methods reported in literature (*Liebigs Ann.* 1996, 1743 - 1749).

Even more advantageously, salts (IA) can be used for the preparation of reactive derivatives of general formula (III), which can be isolated or used *in situ* in the acylation reactions to obtain cephalosporanic antibiotics, such as Cefdinir, Cefdaloxime and other third and fourth generation cephalosporins, according to the procedures described in literature (US 6,093,814, *Organic Process Research & Development* 1997, 1 121-123).

(III)



In compounds of formula (III), Q and R are as described above, and Z is a carboxy-activating group which, together with the C=O group to which it is bound, forms:

1. a mixed anhydride of formula -C(O)-O-P(O)$(OR_1)_2$ wherein R_1 is an aryl group or a C_1-C_6 straight or branched alkyl group; a preferred anhydride is the anhydride with diethylphosphoric acid of formula -C(O)-O-P(O)$(OEt)_2$ (*Synthetic Communication*, 28(1), 1998, 35-44);
2. a mixed anhydride of formula -C(O)-O-P(S)$(OR_1)_2$ wherein R_1 is as defined above; a preferred anhydride is that with diethylthiophosphoric acid, of formula -C(O)-O-P(S)$(OEt)_2$ (EP 0812846);
3. a mixed anhydride of formula -C(O)-O-SO_2R_1 wherein R_1 is as

defined above; a preferred mixed anhydride is that with *para*-toluenesulfonic acid, of formula $-C(O)-O-SO_2(p-C_6H_4)CH_3$ (US 5,589,594);

4. a mixed anhydride of formula $-C(O)-O-COR_1$ wherein R_1 is as defined above; a preferred mixed anhydride is that with pivalic acid, of formula $-C(O)-O-COC(CH_3)_3$;

5. a mixed anhydride of formula $-C(O)-O-CO_2R_1$ wherein R_1 is as defined above; a preferred mixed anhydride is that with ethylcarbonic acid, of formula $-C(O)-O-CO_2Et$;

6. a reactive ester of formula $-C(O)-O-R_2$ wherein R_2 is an aryl or heterocyclic residue such as pentacloro-1-phenyl, benzotriazol-1-yl, N-succinimido, N-phthalimido; preferred is the ester with 1-hydroxybenzotriazole (*The Journal of Antibiotics,* 1990, 43(12), 1564 - 1572);

7. a thioester of formula $-C(O)-S-R_3$ wherein R_3 is a heterocyclic residue selected from 2-pyridyl, benzothiazol-2-yl, benzoxazol-2-yl, benzimidazol-2-yl; preferred is the thioester with 2-mercaptobenzothiazole (EP 0037380, EP 0849269);

8. a reactive amide of formula $-C(O)NR_3R_4$ wherein NR_3R_4 is the residue of a nitrogen heterocycle selected from imidazolyl, 1,2,4-triazolyl, tetrazolyl, benzotriazolyl; preferred is the amide with benzotriazol-3-oxide-1-yl (*The Journal of Antibiotics*, 1993, 46(2), 359 - 361);

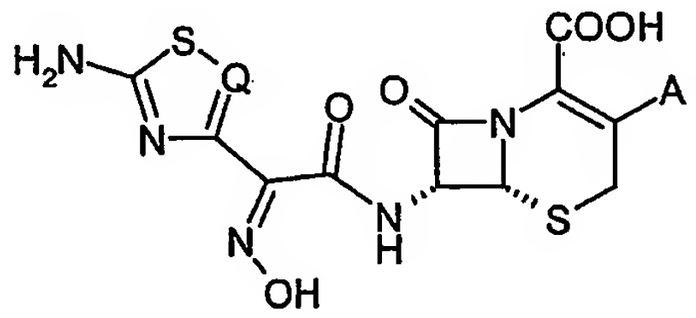
9. an acid chloride of formula $-C(O)Cl$, wherein the amino group of compound (I) can be free or in the form of salt with a mineral or organic acid (US 6,030,965).

Compared with acids of formula (I), salts (IA) are usually more soluble in the organic solvents traditionally used for the activation reactions, such as

methylene chloride, ethyl acetate and tetrahydrofuran, and the reactions are usually faster, give higher yields and yield compounds of formula (III) having higher purity.

Salts (IA) allow therefore to carry out a process for the preparation of cephalosporins of general formula (IX),

(IX)



comprising the conversion of a salt of formula (IA) into a compound of formula (III), the reaction of the latter with a suitable 7-amino-cephalosporanic acid derivative and the subsequent deprotection of the hydroxy-imino residue.

In compounds of formula (IX), Q is as defined above and A is a typical residue of cephalosporins chemistry, preferably vinyl, (-CH=CH_2) or methoxymethylene (-CH_2-O-CH_3).

According to a preferred embodiment of the process of the invention, compounds (IX) Cefdinir, wherein Q is the hydrocarbyl residue (-CH) and A is vinyl, and Cefdaloxime, wherein Q is the hydrocarbyl residue (-CH) and A is methoxymethylene, are prepared.

The following examples illustrate the invention in greater detail.

EXAMPLES

Example 1 - Preparation of (Z)-2-(2-aminothiazol-4-yl)-2-trityloxyimino acetic acid triethylammonium salt.

To a suspension of 200 g of (Z)-2-(2-aminothiazol-4-yl)-2-hydroxymmino acetic acid in 2.2 liters of sulfolane and 500 ml of triethylamine, heated at 84÷90°C, 297 g of triphenylchloromethane dissolved in 1300 ml of toluene was added in 2.5 hours under strong stirring. The

reaction mixture was kept under vigorous stirring at 85÷90°C for 1 hour. The suspension was cooled to 20°C and filtered after 1.5 hour. The solid was washed with water and toluene, then dried to obtain 475 g of (Z)-2-(2-aminothiazol-4-yl)-2-trityloxyimino acetic acid triethylammonium salt.

IR $(KBr)_{cm-1}$: 3440 -3230, 3054, 1610.

^{1}H-NMR (300MHz, DMSO-d_6) δ:7.45÷7.10 (15H, mm, phenyl-H); 7.00 (2H, s, -NH_2); 6.50 (1H, s, thiazole-H); 2.97 (6H, q, -CH2 triethylamine); 1.14 (9H, t, -CH_3 triethylamine).

Following the procedure described in Example 1, but replacing triethylamine with the suitable organic base, the following compounds were obtained:

- (Z)-2-(2-aminothiazol-4-yl)-2-trityloxyimino acetic acid tributylammonium salt;
- (Z)-2-(2-aminothiazol-4-yl)-2-trityloxyimino acetic acid N-methyl morpholinium salt;
- (Z)-2-(2-aminothiazol-4-yl)-2-trityloxyimino acetic acid N-methyl pyrrolidinium salt;
- (Z)-2-(2-aminothiazol-4-yl)-2-trityloxyimino acetic acid N-methyl piperidinium salt.

Example 2 - Preparation (Z)-2-(2-aminothiazol-4-yl)-2-trityloxyimino acetic acid.

To a suspension of 200 g of (Z)-2-(2-aminothiazol-4-yl)-2-hydroxyimino acetic acid in 2.2 liters of sulfolane and 500 ml of triethylamine, heated at 85÷90°C, 297 g of triphenylchloromethane dissolved in 1300 ml toluene were added, under vigorous stirring in 2.5 hours. The reaction mixture was kept under vigorous stirring at 84÷90°C for 1 hour. The suspension was cooled to 20°C and filtered after 1.5 hour. After washing with water, the solid was taken up into 150 ml of purified water and 1100 ml of

ethanol. The suspension was heated to 50°C and a further 1100 ml of ethanol was added in 30 minutes. The mixture was gradually cooled to 10°C in an hour, acidified to pH 4.0 by addition of 20% hydrochloric acid, then kept for an hour at 10°C and filtered. The solid was washed with water and dried to obtain 366 g of (Z)-2-(2-aminothiazol-4-yl)-2-trityloxyimino acetic acid.

IR and NMR analysis, compared with the data reported in literature (Kamachi et al., *The Journal of Antibiotics*, 1990, 1564-1572), confirmed the structure of the product.

Example 3 - Purification of (Z)-2-(2-aminothiazol-4-yl)-2-trityloxyimino acetic acid triethylammonium salt.

A suspension of 150 g of (Z)-2-(2-aminothiazol-4-yl)-2-trityloxyimino acetic acid triethylammonium salt in 600 ml of toluene was heated to 65°C and left under stirring at 65°C for 60 minutes. The suspension was then cooled to 5°C and filtered after an hour. The solid was washed with toluene and dried under vacuum at 65°C for 12 hours, to obtain 134 g of (Z)-2-(2-aminothiazol-4-yl)-2-trityloxyimino acetic acid triethylammonium salt.

Example 4 - Purification of (Z)-2-(2-aminothiazol-4-yl)-2-trityloxyimino acetic acid triethylammonium salt.

A suspension of 300 g of (Z)-2-(2-aminothiazol-4-yl)-2-trityloxyimino acetic acid triethylammonium salt in 600 ml of purified water was cooled to 10°C and left under stirring for 2 hours. The suspension was then cooled to 2°C and filtered after an hour. The solid was washed with water, then dried to obtain 192 g of (Z)-2-(2-aminothiazol-4-yl)-2-trityloxyimino acetic acid triethylammonium salt.

Example 5 - Preparation of 2-benzothiazolyl-(Z)-2-(2-aminothiazol-4-yl)-2-trityloxyimino thioacetate.

To a suspension of 310 g of bis(2-mercaptobenzothiazolyl) disulfide in 2250 ml of methylene chloride at room temperature, 244 g of

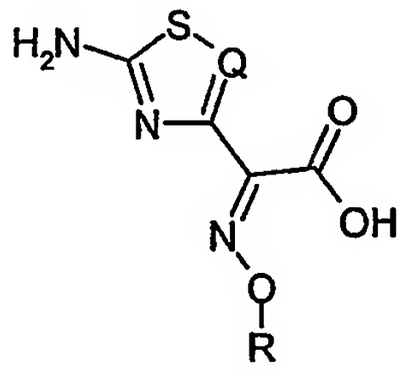
triphenylphosphine was added and the suspension was kept for 30 minutes under stirring at 21°C. Afterwards, 465 g of (Z)-2-(2-aminothiazol-4-yl)-2-trityloxyimino acetic acid triethylammonium salt were added to the suspension in 5 minutes. Temperature raised to 27°C. The suspension was kept at 23÷25°C for 90 minutes, then filtered and the solid was washed with methylene chloride and dried to obtain 456 g of 2-benzothiazolyl-(Z)-2-(2-aminothiazol-4-yl)-2-trityloxyiminothioacetate.

NMR analysis, compared with the data reported in literature (Wollmann et al., *Liebigs Ann.*, 1996, 1743-1749), confirmed the structure of the product.

^{1}H-NMR (300MHz, DMSO-d_6) δ:8.30÷8.24 (1H, d), 8.13÷8.07 (1H, d), 7.63÷7.53 (2H, m); 7.40÷7.20 (17H, m); 6.83 (1H, s).

CLAIMS

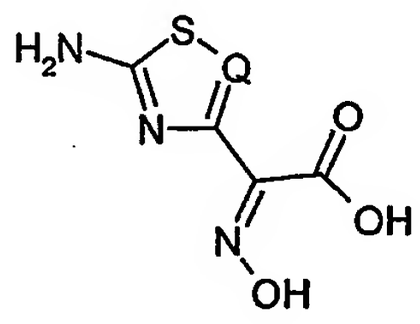
1. A process for the preparation of salts of organic nitrogen bases with carboxylic acids of general formula (I)

(I) 

wherein:

- Q is nitrogen, a hydrocarbyl (CH) or chlorocarbyl (CCl) residue;
- R is trityl, benzhydryl or para-methoxy benzyl;

which process comprises reacting a carboxylic acid of general formula (II)

(II) 

wherein Q has the meaning defined above,

with a halide of formula (V)

(V) RX

wherein R has the meaning defined above and X is a halogen selected from chlorine, bromine and iodine,

in the presence of a nitrogen organic base and of an organic inert solvent.

2. A process as claimed in claim 1, wherein the nitrogen organic base is a tertiary amine selected from triethylamine, tributylamine, N-ethyl disopropylamine, N-methyl morpholine, N-methyl pyrrolidine, N-methylpiperidine, trioctylamine.

3. A process as claimed in claim 1 wherein the nitrogen organic base is an amidine selected from diazabicyclononene (DBN) and diazabicycloundecene

(DBU).

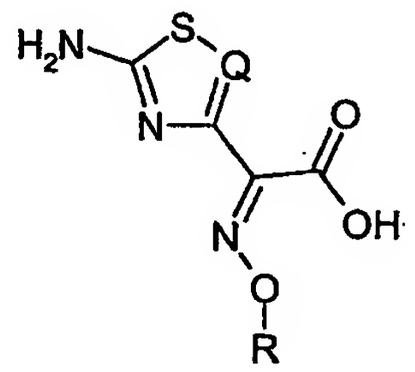
4. A process as claimed in claim 1 wherein the organic base is tetramethyl guanidine.

5. A process as claimed in any one of the above claims wherein the inert organic inert solvent is selected from halogenated hydrocarbons, carboxylic acid esters, ketones, amides, aromatic hydrocarbons, ethers, sulfoxides or sulfones, or mixtures thereof.

6. A process as claimed in claim 5 wherein the inert organic solvent is selected from methylene chloride, dichloroethane, ethyl acetate, butyl acetate, acetone, diethyl ketone, methyl-ethyl ketone, N,N-dimethylformamide, N,N-dimethylacetamide, N-methylpyrrolidone, benzene, toluene, xylene, tetrahydrofuran, dioxane, ethylene glycol dimethyl ether, dimethylsulfoxide, dimethyl sulfone and sulfolane or mixtures thereof.

7. A process as claimed in any one of the above claims, further comprising the transformation of the salts as defined in claim 1 into the respective carboxylic acids (I).

8. Salts of organic nitrogen bases with carboxylic acids of general formula (I)



(I)

wherein:

- Q is nitrogen, a hydrocarbyl (CH) or chlorocarbyl (CCl) residue;
- R is trityl, benzhydryl or para-methoxy benzyl.

9. Salts as claimed in claim 8 wherein the nitrogen organic base is a tertiary amine selected from triethylamine, tributylamine, N-ethyl diisopropylamine, N-methyl morpholine, N-methyl pyrrolidine, N-methyl piperidine, trioctylamine.

10. Salts as claimed in claim 8 wherein the nitrogen organic base is an amidine selected from diazabicyclononene (DBN) and diazabicycloundecene (DBU).

11. Salts as claimed in claim 8 wherein the nitrogen organic base is tetramethyl guanidine.

12. Salts as claimed in claim 9 selected from:

(Z)-2-(2-aminothiazol-4-yl)-2-trityloxyimino acetic acid triethylammonium salt;

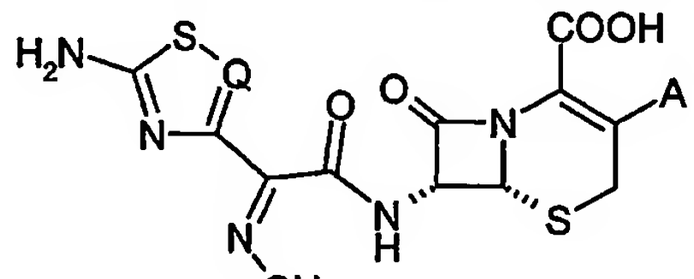
(Z)-2-(2-aminothiazol-4-yl)-2-trityloxyimino acetic acid tributylammonium salt;

(Z)-2-(2-aminothiazol-4-yl)-2-trityloxyimino acetic acid N-methyl morpholinium salt;

(Z)-2-(2-aminothiazol-4-yl)-2-trityloxyimino acetic acid N-methyl pyrrolidinium salt;

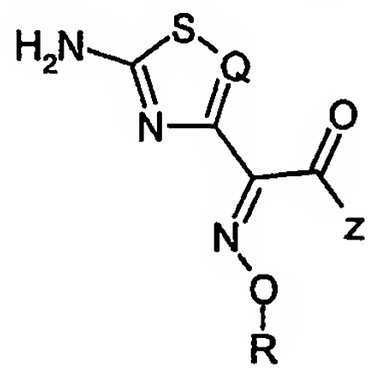
(Z)-2-(2-aminothiazol-4-yl)-2-trityloxyimino acetic acid N-methyl piperidinium salt.

13. A process for the preparation of cephalosporins of general formula (IX),



(IX)

wherein Q is as defined in claim 1 and A is a vinyl or methoxymethylene residue, which process comprises reacting a derivative of formula (III),



(III)

wherein Q and R are as defined in claim 1, and Z is a carboxy-activating group,

with a 7-amino-cephalosporanic acid and subsequently deprotecting the hydroxy-imino residue,

characterized in that derivative of formula (III) is obtained from the salt of claims 8 -12.

14. A process as claimed in claim 13, wherein in compounds of formula (III) Z is a carboxy-activating group which, together with the C=O group to which it is bound, forms:

- a mixed anhydride of formula $-C(O)-O-P(O)(OR_1)_2$ wherein R_1 is an aryl group or a C_1-C_6 straight or branched alkyl group;
- a mixed anhydride of formula $-C(O)-O-P(S)(OR_1)_2$ wherein R_1 is as defined above;
- a mixed anhydride of formula $-C(O)-O-SO_2R_1$ wherein R_1 is as defined above;
- a mixed anhydride of formula $-C(O)-O-COR_1$ wherein R_1 is as defined above;
- a mixed anhydride of formula $-C(O)-O-CO_2R_1$ wherein R_1 is as defined above;
- a reactive ester of formula $-C(O)-O-R_2$ wherein R_2 is an aryl or heterocyclic residue selected from pentacloro-1-phenyl, benzotriazol-1-yl, N-succinimido, N-phthalimido;
- a thioester of formula $-C(O)-S-R_3$ wherein R_3 is a heterocyclic residue selected from 2-pyridyl, benzothiazol-2-yl, benzoxazol-2-yl, benzimidazol-2-yl;
- a reactive amide of formula $-C(O)NR_3R_4$ wherein NR_3R_4 is the residue of a nitrogen heterocycle selected from imidazolyl, 1,2,4-triazolyl, tetrazolyl, benzotriazolyl;

- an acid chloride of formula -C(O)Cl, wherein the amino group of compound of formula (I) can be free or in the form of a salt with a mineral or organic acid.

15. A process as claimed in claims 13 and 14, wherein in compounds formula (IX) Q is a hydrocarbyl residue (-CH) and A is a vinyl residue (-CH=CH_2).

16. A process as claimed in claims 13 and 14, wherein in compounds of formula (IX) Q is a hydrocarbyl residue (-CH) and A is a methoxymethylene residue (-CH_2-O-CH_3).